CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

August 22, 1997

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens (MD WC-05)
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Review of 1,3-Butadiene Classification for the Report on Carcinogens, Ninth Edition

Dear Dr. Jameson:

The Chemical Manufacturers Association (CMA) Olefins Panel (Panel) is pleased to submit these comments in response to the National Toxicology Program (NTP) request for input to its review of 1,3-butadiene classification for the Report on Carcinogens, Ninth Edition. 62 Fed. Reg. 37272 (July 11, 1997). Members of the Olefins Panel include the major domestic producers and some users of butadiene.[1]

Since 1991, the Panel has sponsored a comprehensive research program on butadiene to develop an understanding of species differences in response to butadiene and to provide a scientifically sound basis for assessing potential human health risks from exposures to butadiene in the workplace and the general population. The Panel also has sponsored symposia on butadiene toxicology and epidemiology and is coordinating with the research efforts of other organizations.

The International Institute of Synthetic Rubber Producers (IISRP) separately is submitting comments to NTP. The Panel joins with IISRP in urging NTP to consider the recent butadiene toxicology reviews by Himmelstein *et al.* (1997) and by the European Centre for

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1 Members of the Panel include: Amoco Chemical Company; BP Chemicals, Inc.; Chevron Chemical Company; The Dow Chemical Company; DuPont; Eastman Chemical Company; Exxon Chemical Americas; Huntsman Corporation; Lyondell Petrochemical Company; Occidental Chemical Corporation; Shell Oil Company, and Union Carbide Corporation.

Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997).[2] These documents help elucidate the findings of the recent epidemiology study of styrene-butadiene rubber (SBR) manufacturing workers conducted by Dr. Delzell *et al.*. (1996).[3] The reviews also discuss the extensive animal study database for butadiene.

The Panel believes that there are significant issues regarding the potential carcinogenicity of butadiene in humans. For example, the absence of an observed leukemia excess in butadiene monomer workers raises the possibility that the excess leukemias reported by Delzell *et al.* were due to a cofactor or a confounding factor. As described in the letter submitted by IISRP, this topic of possible confounders was discussed at the recent Toxicology Forum in July 1997, and the published proceedings from that session will be provided when they become available. In addition, significant metabolic and effect differences among species must be considered when using animal data to evaluate the potential for human carcinogenicity due to butadiene exposure.

Enclosed with these comments is a brochure describing the Panel's butadiene research program. The Panel believes it is important that NTP consider the entire animal and human database, as well as the outstanding issues that are being addressed by ongoing research. The Panel will provide additional research results to NTP as they become available.

The Panel appreciates this opportunity to comment and looks forward to continuing dialogue with NTP as it reviews butadiene. If you have any questions, please call Dr. Elizabeth J. Moran, Manager of the Olefins Panel, at (703) 741-5617.

Sincerely yours,

Courtney Price

Courtney M. Price
Vice-President, CHEMSTAR

Attachment

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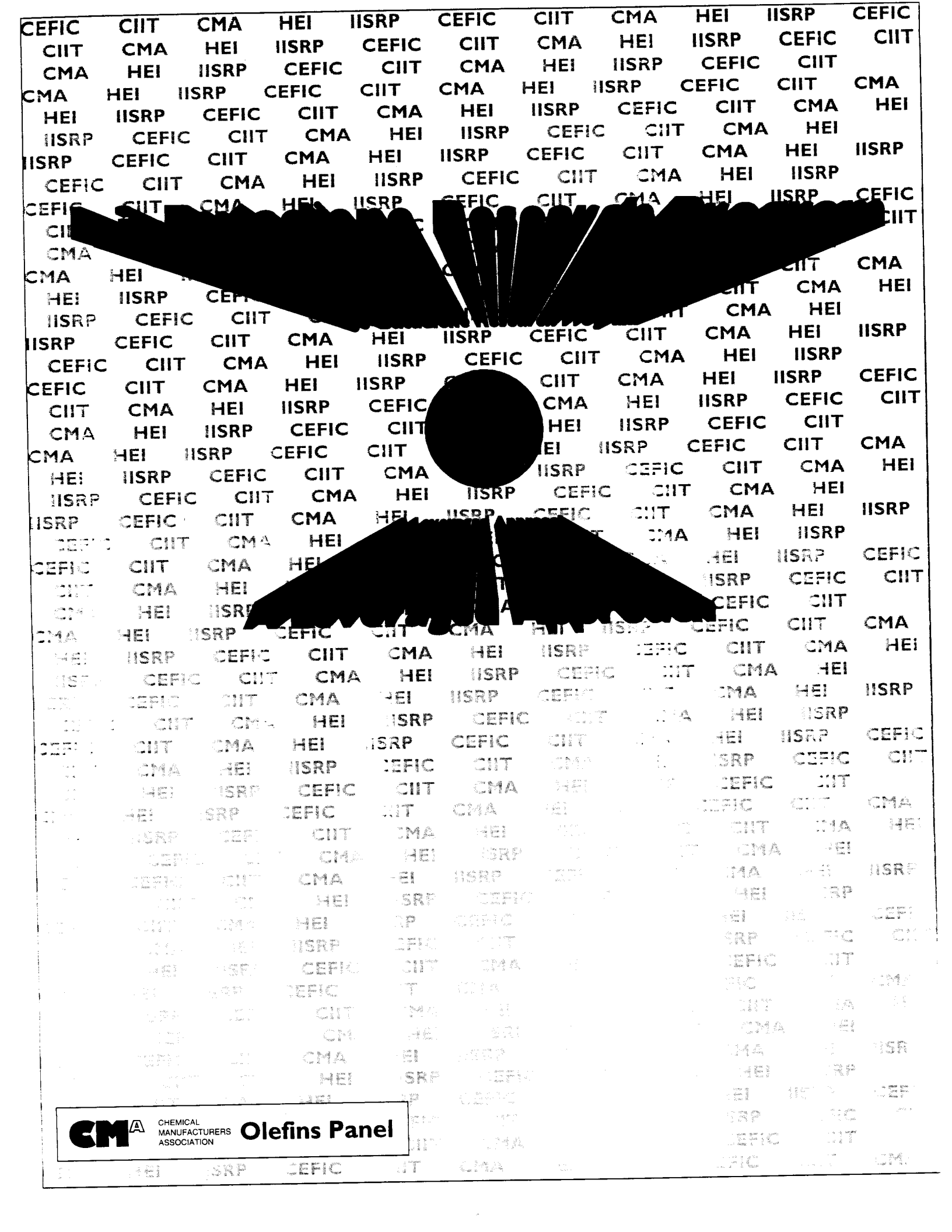
2 M.W. Himmelstein, *et al.* (1997). Toxicology and Epidemiology of 1,3-Butadiene. *Critical Reviews in Toxicology* 27:1-108; ECETOC (1997). *1,3-Butadiene OEL Criteria Document (Second Edition), CAS No. 106-99-0.* Special Report No. 12 (Brussels, Belgium). Both of these documents are being provided with the IISRP comments.

3 E. Delzell *et al.* (1996). Follow-up Study of Synthetic Rubber Workers. *Toxicology* 113:182.


CEFIC CIIT CMA HEI IISRP
CHEMICAL MANUFACTURERS ASSOCIATION
Olefins Panel

Overview

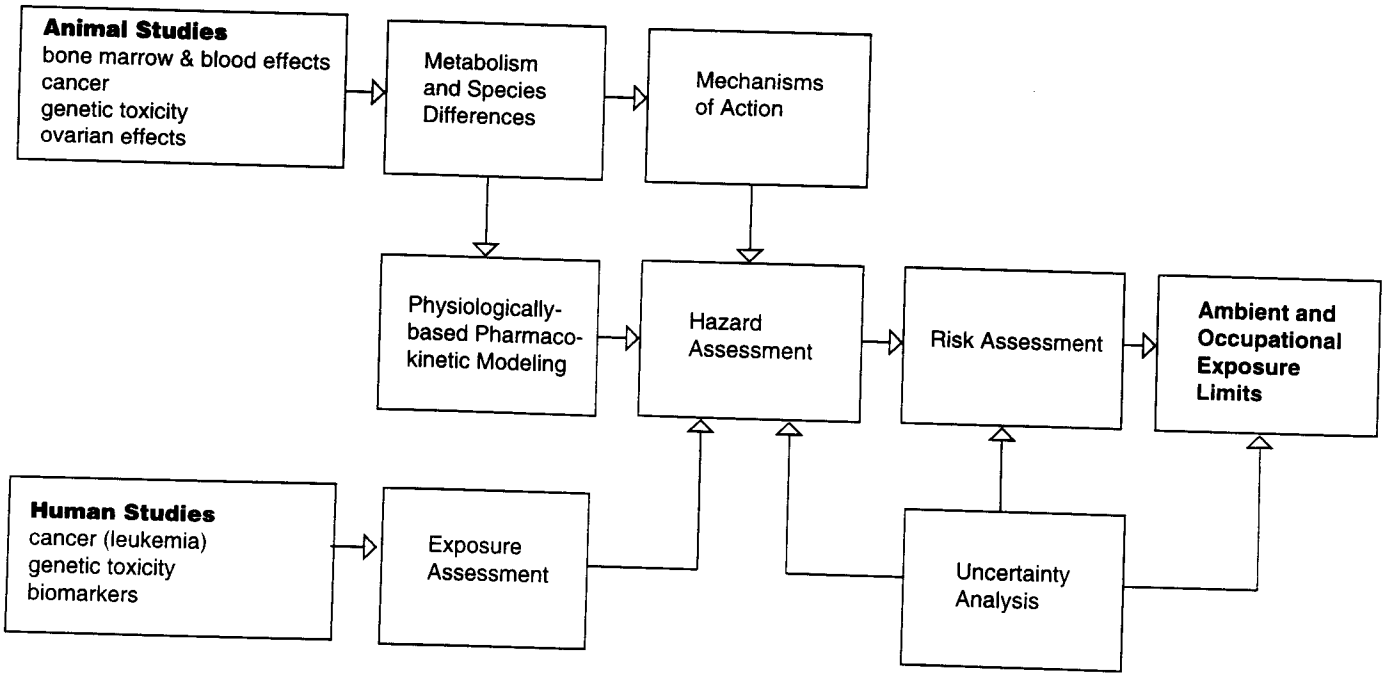
In 1991, the Chemical Manufacturers Association Olefins Panel began a comprehensive research program on 1,3-butadiene involving four research centers. At that time, health effects studies of 1,3-butadiene indicated a potent carcinogenic effect in the mouse, a weak response in the rat and equivocal findings in humans. The Panel focused on developing an understanding of the basis for the apparent species differences in response. The Panel believe that differences in carcinogenic susceptibility must be understood before meaningful estimations of risk to humans could be made. Since then, species differences, bone marrow effects and mechanisms of action have been examined.

In 1995, an International Symposium was held in Blaine, Washington to discuss recent findings. Organizations conducting research on 1,3-butadiene from around the world attended. A University of Alabama study indicated an increase in leukemia associated with working in the styrene-butadiene rubber industry. The Panel's research program has been refocused to provide a scientifically sound basis for assessing potential human health risks from exposures to butadiene under various scenarios, primarily workplace and general population. Research on butadiene also is being conducted by the Chemical Industry Institute of Toxicology (CIIT), the European Chemical Industry Council (CEFIC), the Health Effects Institute (HEI), and the International Institute of Synthetic Rubber Producers (IISRP). These research efforts have been coordinated to form a comprehensive research approach.

What Is Butadiene?

1,3-Butadiene, a flammable, colorless gas, is used extensively in the production of polymers and synthetic rubber. Butadiene also is formed during the incomplete combustion of petroleum-derived fuels, in particular, by gasoline and diesel powered motor vehicles.

Program Elements and Interface



Current Focus

The Butadiene Research Program under the Olefins Panel (the Panel) had been focused on understanding the relevance of the animal data to human risk assessment by examining species differences, bone marrow effects and mechanisms of action. The bone marrow studies showed that the mouse leukemia/lymphoma model is not relevant to humans. Profound species differences in metabolism of butadiene led to the hypothesis that the diepoxide metabolite is the primary carcinogenic metabolite in the mouse. Data from mouse and rat metabolism studies were used to develop a physiologically-based pharmacokinetic model.

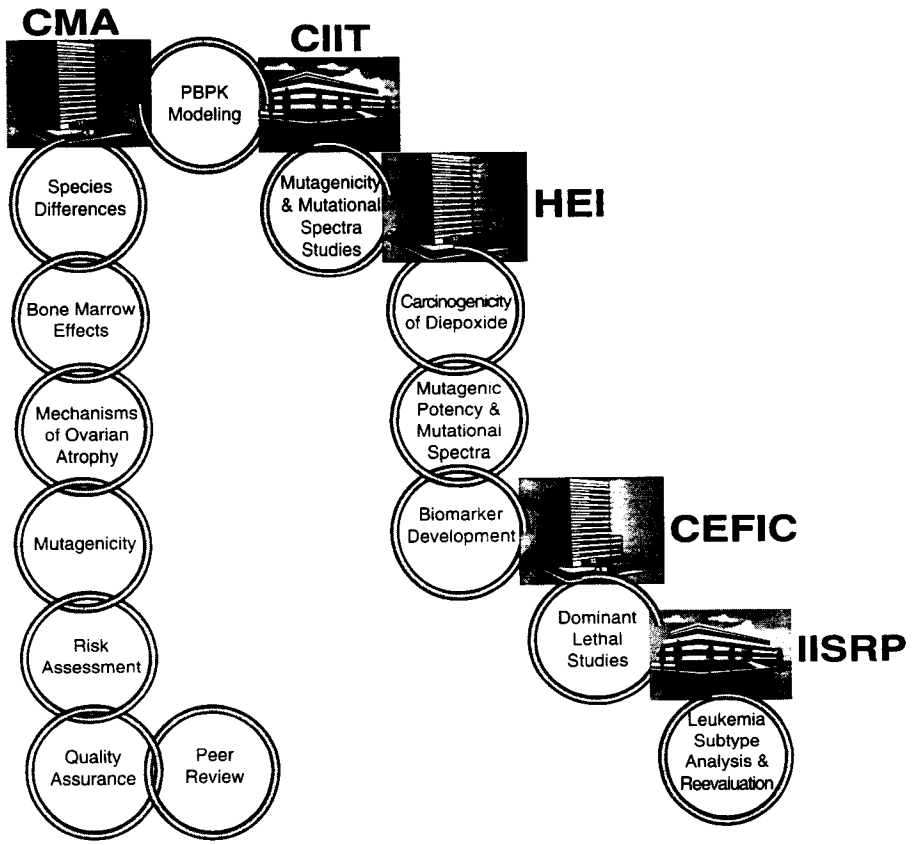
With the publication of the University of Alabama (UAB) epidemiology study, the CMA Butadiene Research Program was refocused to understand and supplement these new findings. Although UAB found an increase in leukemia in the styrene-butadiene rubber industry, recently published epidemiology studies in butadiene production workers, although in smaller populations, did not show increases in leukemia. Bone marrow studies are being refocused to determine whether they can shed any light on these epidemiology findings.

The Panel is continuing to develop the PBPK model, expanding the model to predict metabolite levels in humans. In addition, the Panel is exploring whether the model can be used to test some of the hypothesis on dose-response raised by the epidemiology studies. The Panel has continued to support mechanistic studies to understand the relevance to humans of ovarian atrophy found in the mouse.

The Olefins Panel has also worked to develop a comprehensive research approach among the many groups interested in butadiene risk assessment. Thus, while the Panel has taken the lead in understanding the animal cancer studies, CEFIC has taken the lead in understanding dominant lethal and teratogenic effects in mice and their relevance to humans. Similarly, HEI has developed an extensive mutagenicity program, and the Panel has discontinued work in this area. IISRP is expanding and reevaluating the exposure component of the UAB study and looking at factors that are specific to SBR operations and processes. They are sponsoring work to understand better the role of continuous low dose versus short term peak exposures in development of leukemia. The Olefins Panel is using data from the UAB study to develop dose response models for risk assessment.

The components of the Butadiene Research Program are listed in the box on the next page. Descriptions of the other programs are included on page 9. Together, the components of all the programs address the questions that need to be understood to develop a better model for human risk assessment.

Program Sponsor Interfaces



The Olefins Panel
Butadiene Research Program

Program	Research Center
Species Differences	Lovelace Respiratory Research Institute
Physiologically-based Pharmacokinetic Modeling	Chemical Industry Institute of Toxicology
Bone Marrow Effects	University of Colorado
Mechanism of Ovarian Atrophy	University of Arizona
Mutagenicity	University of North Carolina
Risk Assessment	ChemRisk Sielken, Inc.
Quality Assurance	Baldwin Consulting
Peer Review	Drs. Albertini, Birnbaum, Guengerich, and Weirda

Species Differences

Lovelace Respiratory Research Institute

In mice and rats, exposure to 1,3-butadiene leads to the formation of two epoxide metabolites, the monoepoxide (1,2-epoxy-3-butene) and the diepoxide (1,2,3,4-diepoxybutane). However, when exposed to the same butadiene concentration, mice and rats differ in the relative amounts of the two epoxide metabolites. Mice produce 4 to 10 times more monoepoxide and 40 to 100 times more diepoxide than the rat. In studies conducted at the University of North Carolina, the diepoxide was found to be 100 times more mutagenic than the monoepoxide. Taken together, these findings lead to the hypothesis that the diepoxide is the primary ultimate carcinogen in mice.

This program focuses on differences in butadiene metabolism in mice, rats, monkeys and humans and relates them to observed differences in sensitivity to the carcinogenicity of the chemical. The most sensitive species, the mouse, forms more toxic metabolites of butadiene and breaks them down less efficiently than the other species. Mice, rats and primates will be exposed to butadiene and the build up of butadiene and its metabolites in blood and tissues will be monitored after single and repeated exposure at several dose levels. These studies will aid in determining if metabolism contributes to species differences in sensitivity and in extrapolating animal carcinogenicity data to predicted risks for humans.

Findings: Two recent findings with regard to the highly mutagenic metabolite, butadiene diepoxide, were made. Rats exposed over a range of two orders of magnitude of butadiene concentrations had approximately the same low blood and tissue levels of the diepoxide. Butadiene-exposed female rats were found to have approximately five times the concentration of diepoxide in tissues as males. The lack of linearity in the exposure-dose relationship and the gender differences in metabolism are important considerations for risk assessments for butadiene, based on rat studies. Studies of the effect of repeated low-concentration exposures on the metabolism of butadiene in rats and mice indicated some accumulation of metabolites in fatty tissues but little induction of metabolism. ***Rogene Henderson, Ph.D. is the principal investigator.***

Physiologically-based Pharmacokinetic Modeling

Chemical Industry Institute of Toxicology

This program is aimed at developing a human physiologically-based pharmacokinetic model for inhaled butadiene. A rodent dosimetry model is being developed that will serve as the basis for the human dosimetry model. The physiologically-based pharmacokinetic model that is being developed will improve the estimation of dose at the target site. Moreover, the model will enable (1) scaling of dose across species (e.g., animals to humans), (2) extrapolation from high-to-low exposure concentrations, and (3) estimation of internal dose derived from different exposure scenarios (e.g., long-term low level vs. short-term high level). This information is needed to improve human health risk estimates from butadiene exposure. The dosimetry models will incorporate much of the data being generated at all panel-sponsored research centers.

Findings: A rat and mouse refined dosimetry model was developed. There are several key features of the refined model that distinguish it from other butadiene dosimetry models. These

features include (1) inclusion of the lung as a metabolizing organ for butadiene, (2) use of partition coefficients for butadiene, epoxybutene, and diepoxybutane, and (3) incorporation of *in vitro* kinetic constants for oxidation of butadiene and epoxybutene and detoxication via hydrolysis and glutathione conjugation of epoxybutene and diepoxybutane. This refined model accurately predicts blood levels of butadiene, epoxybutene, and diepoxybutane in rats and mice exposed by inhalation to butadiene. The next step is to use this refined rodent dosimetry model to develop a preliminary human dosimetry model using in vitro kinetic constants from human tissues. ***James Bond, Ph.D., is the principal investigator.***

Bone Marrow Effects

University of Colorado

The program was originally aimed at understanding the marked species differences in susceptibility of leukemia/lymphoma associated with chronic exposure to butadiene. Although certain strains of mice are extremely susceptible to butadiene-induced lymphoma, chronic exposure of the rat to butadiene does not result in an increase in leukemia or lymphoma.

In the mouse bone marrow, butadiene targets a subpopulation of undifferentiated stem cells, resulting in their death. The elimination of these cells leads to leukemia/lymphoma in the mouse. This subpopulation of stem cells does not exist in rat or human bone marrow. Therefore, the mouse leukemia/lymphoma finding is not relevant to human risk assessment.

Following release of the UAB results, this program was refocused to test hypotheses generated by the findings. The UAB study suggested an approximately two-fold increase in the relative risk of unspecified leukemias for synthetic rubber workers potentially exposed to high concentrations of 1,3-butadiene. However, no clear dose-response relationship has been established and no increase in leukemia has been observed in workers engaged in monomer production alone. Taken together, these results suggest the possibility that confounding factors may be present that influence the outcomes reported in the study.

Findings: Dimethyl-dithiocarbamate is an example of an agent which is not used in monomer production but is present in the polymerization process. Dithiocarbamates are known inhibitors of cytochrome P450 2E1 and the transcriptional activator, NF-kB. Preliminary studies in this laboratory suggest that dimethyl-dithiocarbamate is over 100 times more toxic to the human $CD34^+$ cells than the most potent butadiene metabolite, epoxybutene. Efforts are underway to further characterize the significance of dimethyl-dithiocarbamate-induced bone marrow toxicity on hematopoietic stem cell differentiation and leukemogenesis. ***Richard Irons, Ph.D. is the principal investigator.***

Ovarian Atrophy

University of Arizona

This program examines the difference in susceptibility of the mouse and rat in butadiene-induced ovarian toxicity. Butadiene exposure results in a dose and time related increase in ovarian atrophy in the mouse. This effect is not seen in the rat. However, epoxide metabolites of butadiene do cause ovarian toxicity in the rat. Recent studies on other chemicals indicate that diepoxide metabolites are implicated in ovarian toxicity and that these diepoxides cause ovarian toxicity by apoptosis. Understanding species differences in the ovarian toxicity of the butadiene metabolites is important to predicting human risk. ***I. Glenn Sipes, Ph.D. is the principal investigator.***

Mutagenicity

University of North Carolina

The research examines the ability of butadiene and its metabolites to form DNA adducts and induce alterations in DNA sequences (mutations). Highly specific and sensitive GC/MS methods are being developed for DNA and Hb adducts of both the mono- and diepoxide of butadiene. These methods will be applied to tissues of rats and mice exposed to butadiene. Hemoglobin adducts will be measured in human red blood cells obtained from two worker populations: one in China and one in the Czech Republic. Comparison of the mono- to diepoxide ratios in rats, mice, and humans may allow determination of the relative extent of metabolism in these species.

Findings: A series of DNA adducts arising from the mono- and diepoxide have been characterized and initial measurements have been made in TK6 cells and in rats and mice. When cells are exposed to the mono- and diepoxide, similar amounts of guanine adducts form. Mice had approximately twice as many adducts as rats. In view of data on the types of mutations induced by butadiene, future studies are focusing on quantitation on N6-adenine adducts in exposed cells and animals. Methods have also been developed to quantitate hemoglobin adducts of the monoepoxide, diolepoxide and diepoxide in rats, mice and humans. ***James Swenberg, D.V.M., Ph.D. is the principal investigator.***

Risk Assessment

ChemRisk

ChemRisk has developed a diepoxide component of the physiologically-based pharmacokinetic model for butadiene based on the CIIT model and expanding it to include diepoxide results. The model also includes a human component so that levels of metabolites following human exposure to butadiene can be calculated. These results can be used to base the risk assessment for 1,3-butadiene on doses of specific metabolites in humans. Dr. Richard Melnick is the principal investigator.

Sielken, Inc.

Sielken, Inc. has used decision analysis methodology and the animal data to explore the effect on risk assessment of using different proposed mechanisms of carcinogenicity. His approach incorporates the results of the human PBPK model, developed by ChemRisk. In addition, Dr. Sielken is examining the dose-response relationships, using the UAB data, to determine whether that data base can be used for risk assessment. Dr. Sielken also has used the PBPK model and the animal data on ovarian atrophy in non-cancer risk assessment. Dr. Robert Sielken is the principal investigator.

Quality Assurance and Peer Review

Quality Assurance

Dr. Judith Baldwin
Baldwin Consulting Services

The Quality Assurance function continues to support the production of data with documented quality. Data from this program are used in discussions with regulatory agencies to provide an appropriate and scientific interpretation of butadiene's mechanism of action and species response differences.

Assessment focus continues on validation and verification of analytical results. Examination of method limits of detection facilitates comparison and integration of data from the various participants in this research program. Confidence in values obtained from different analytical methods has contributed to the evaluation of biological relevance of program data against other published data. Such confidence is supported by documentation that meets or exceeds contemporaneous standards and a continuing independent evaluation of that documentation.

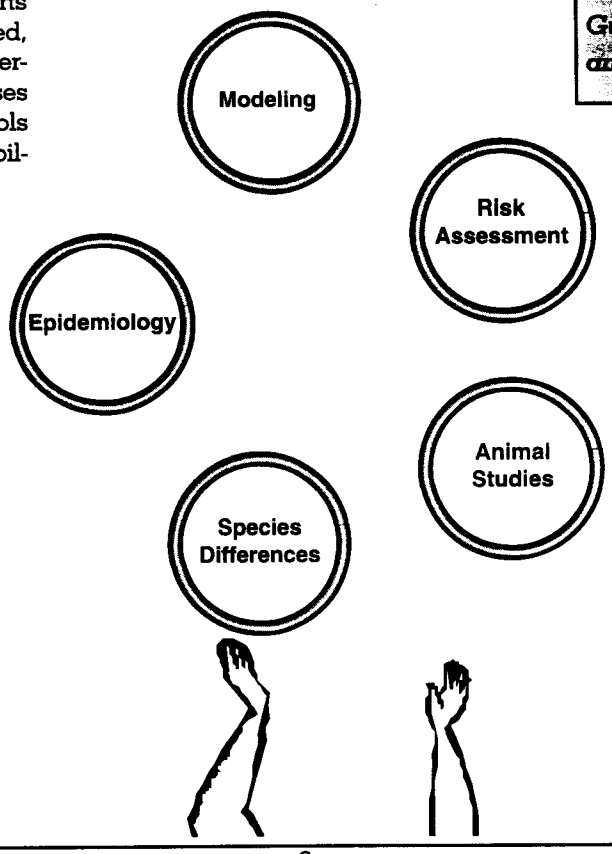
Quality Assurance functionally supports cooperative efforts in this multi-centered, multi-disciplinary approach to the understanding of complex metabolic processes in various species. Plans and protocols have been reviewed to reduce variability and to optimize design.

Quality Assurance actions have provided continual assessment of program progress in data and documentation quality. Reduction of variability or bias has been achieved through standardization, analysis of accuracy, precision, sensitivity and representativeness. Utilization of basic, cost-effective documentation consisted with the EPA TSCA Good Laboratory Practices Standards (GLPs) continues to be the basis for assessment. In addition to analytical values, the other key areas of evaluation include test system observations, collection and identification of specimens, data handling and retrieval, and confirmation of data transformation by recalculation.

As publications are prepared, Quality Assurance reviews are conducted to ensure that these reports accurately and completely reflect the data and its development. This part of the effort will be expected to intensify in preparation for the program annual research meeting.

Peer Review

An [illegible] quality assurance review [illegible] ongoing through quarterly assurance consultations with staff. [illegible] the research results are [illegible] peer reviewed journals, to ensure the production of high quality research. [illegible] the Olefins Panel has established a Peer Review Advisory Group to provide advice and counsel during all phases of the research program. Five distinguished scientists were selected from government, industry and academia. Each scientist brings expertise in the fields of hematology, biochemistry, metabolism, genetic toxicology and/or inhalation toxicology, the major areas addressed in the research. This year's peer reviewers were: Dr. Richard Albertini (University of Vermont), Dr. Linda S. Birnbaum (EPA), Dr. F. Peter Guengerich (Vanderbilt University) and Dr. Don Wheeler (Eli Lilly).



Peer Review Advisory Group

Richard Albertini, M.D., Ph.D.

Dr. Richard J. Albertini is a Professor of Medicine, Microbiology and Molecular Genetics at the University of Vermont College of Medicine, and is the Director of the Vermont Cancer Center Genetics Laboratory. He received the M.D. and Ph.D. (Medical Genetics) degrees from the University of Wisconsin. Dr. Albertini's principal research interest involves mechanisms of mutation of human cells, with particular reference to *in vivo* mutations. He developed an assay to quantify and isolate mutations for use in workplace monitoring. He ehas bren involved in studies of environmental mutagenicity/carcinogenicity for more than two decades. Dr. Albertini serves and has served on numerous national and international committees dealing with human environmental health issues, including NIH review boards. He is a pst president and past editor-in-chief of Environmental and Molecular Mutagenesis. Dr. Albertini is a recipient of the Environmental Mutagen Society's Alexander Hollander Aware and the St. George Medal of the American Cancer Society. He is on the editorial board of several scientific journals dealing with environmental issues and is a fellow of Conte Institute for Environmental Health. Dr. Albertini's research is currently supported by the NIH, DOE and private industry. Past support has also come from the EPA.

Linda S. Birnbaum, Ph.D.

Dr. Birnbaum is Director of the Environmental Toxicology Division of EPA's Health Effects Research Laboratory. She received her Ph.D. inMicrobiology from the University of Illinois at Urbana. Previously, Dr. Birnbaum was Hed of the Chemical Disposition Group at NIEHS. She is certified as a Diplomat of the American Board of Toxicology. Dr. Birnbaum is on the editorial board of Toxicology and Applied Pharmacology, Environmental Health Perspectives, Journal of Toxicology and Environmental Health, and AGE. She serves on the faculty of the University of North Carolina at Chapel Hill. Dr. Birnbaum is on Scientific Advisory Committees for NIEHS, NIOSH, CIIT and IPCS. She is a member of the Society of Toxicology, the American Society of Pharmacology and Experimental Therapeutics, the American Aging Association, the American Association for the Advancement of Science, and Sigma Xi. She is a past President of the North Carolina Chapter of the Mechanisms Sections of SOT and a past member of its Education Committee. She has authored more than 170 peer-reviewed publications.

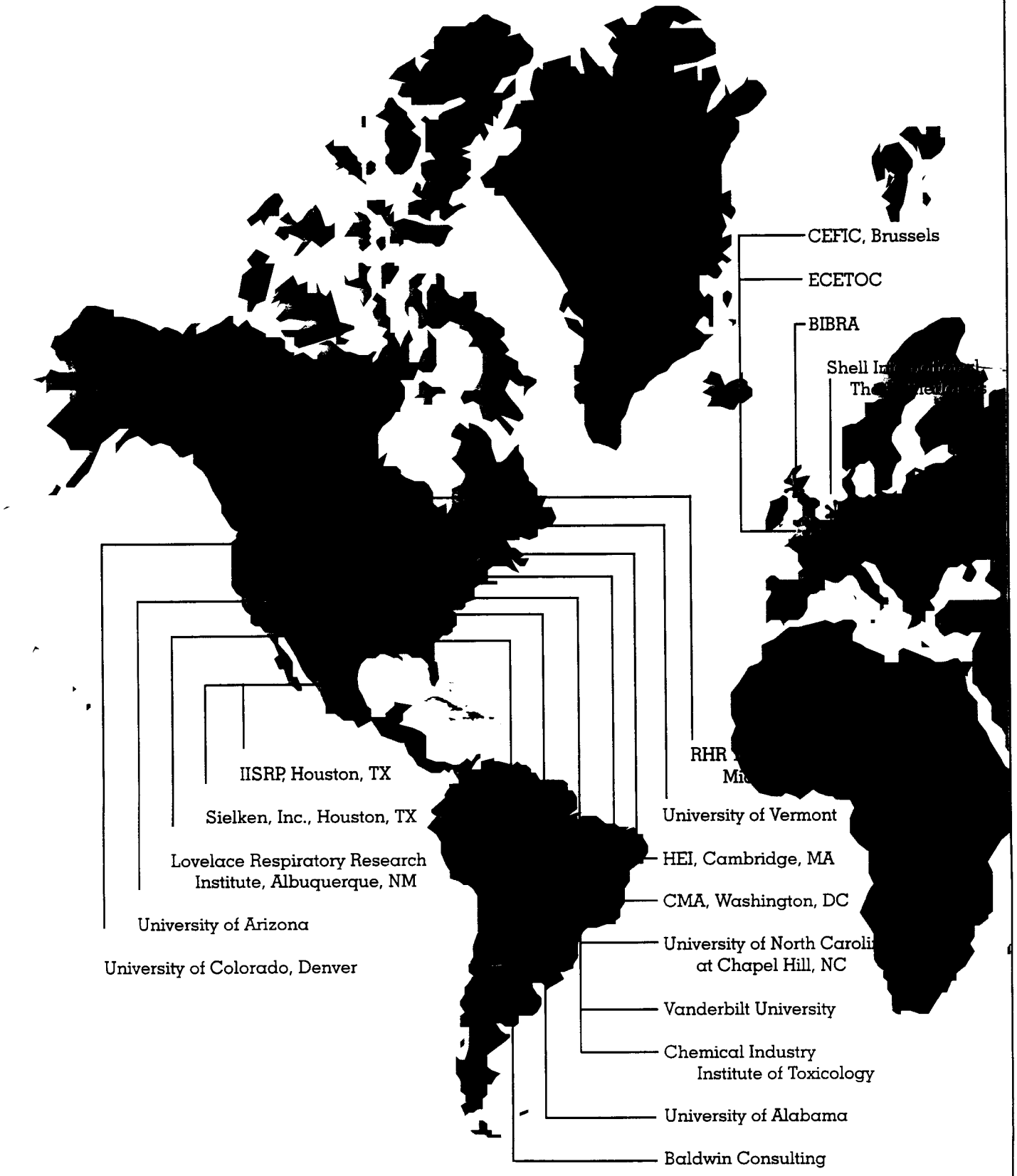
F. Peter Guengerich, Ph.D.

Dr. Guengerich is Professor of Biochemistry and Director of the Center in Molecular Toxicology at Vanderbilt University School of Medicine. He directs the National Institute of Environmental Health Sciences core center grant and training grant, and his own research program is supported by the National Cancer Institute. His research interests involve mechanisms of activation and detoxication of chemical carcinogens and toxicants and the characterization of enzymes involved in these processes. He has served as a member of two National Institute of Health study sections and on other review panels. Professor Guengerich is Associate Editor of Chemical Research in Toxicology and a member of the editorial board of Xenobiotica. Professor Guengerich did his postdoctoral training at The University of Michigan before joining the faculty at Vanderbilt. He received a Ph.D. in Biochemistry from Vanderbilt University.

Dan Wierda, Ph.D.

Dr. Dan Wierda is a research scientist in immunotoxicology with Eli Lilly and Company and an Adjunct Associate Professor of Pharmacology at Indiana University School of Medicine, and at West Virginia University Medical Center. Dr. Wierda received his Ph.D. from the Department of Pharmacology and Toxicology, University of Kansas Medical Center. He performed postdoctoral research at the Chemical Industry Institute of Toxicology. Dr. Wierda is a member of Sigma Xi Research Society, the International Society for Experimental Hematology, the Society of Toxicology, the Ohio Valley SOT, and the SOT Immunotoxicology Specialty Subsection. He is a member of the EPA Grant Review Panel and is a field editor for Fundamental and Applied Toxicology. In the past, Dr. Wierda served on the SOT Program Committee, was a counselor of the specialty subsection and char of the SOT Continuing Education course, "Basic and Applied Hematotoxicity." His research focuses on the immunotoxicity of new pharmaceuticals and biotechnology products.

Location of Butadiene Research Programs



Locations are not exact.

Other Research

Leveraged Research

(Research conducted outside of the CMA Olefins Panel Butadiene Research Program)

Research	Sponsor
Dominant Lethal Studies British Industrial Biological Research Association (BIBRA)	CEFIC & IISRP
Mutagenicity and mutational spectra studies in mouse, rat and human cells and in transgenic mice and rats Chemical Industry Institute of Toxicology (CIIT)	CIIT & HEI
Leukemia subtype analysis and exposure reevaluation University of Alabama	IISRP
Mutagenicity CIIT and NY State Department of Health	HEI
Biomarker Development Vanderbilt University & the University of North Carolina	HEI
Carcinogenicity of Diexpoxide Lovelace Respiratory Research Institute	HEI

Dominant Lethal Studies

European Chemical Industry Council (CEFIC) & International Institute of Synthetic Rubber Producers (IISRP)

The European Community STEP Program and the United Kingdom Health and Safety Executive conducted research on 1,3-butadiene at the British Industrial Biological Research Association (BIBRA). These studies indicate that exposure of male mice to 1,3-butadiene leads to both dominant lethal and teratogenic effects in offspring. Questions about the study results led to a second mouse study at BIBRA. CEFIC and IISRP sponsored a parallel study at BIBRA looking for these effects in the rat.

Findings: The second mouse study indicated that 1,3-butadiene exposure to male mice does result in a dominant lethal effect, but no increase in teratogenic effects was seen. A third mouse study is now being conducted. In contrast, exposure of male rats to 1,3-butadiene did not result in dominant lethal or teratogenic effects. ***Diane Anderson, Ph.D. is the principal investigator.***

Mutational Spectra

Chemical Industry Institute of Toxicology (CIIT)

CIIT is conducting research that is partially funded by the Health Effects Institute. The goal of the research is to determine the mutagenicity and the mutational spectrum of 1,2-epoxy-3-butene and diepoxybutane in human and rodent cells and in transgenic mice and rats. By comparing these spectra with that of butadiene, the relative role of each metabolite in the in vivo genotoxicity of butadiene can be assessed. CIIT is also collaborating with Shell International on a study involving rats and mice exposed to 200 ppm ^{14}C butadiene. The Shell investigators are in the process of analyzing tissues and urine for butadiene metabolites and macromolecular adducts, with the ultimate objective of identifying appropriate butadiene biomarkers for humans. ***James Bond, Ph.D. is the principal investigator.***

Epidemiology

International Institute of Synthetic Rubber Producers (IISRP)

The IISRP sponsors epidemiology research. The University of Alabama conducted a cohort study of approximately 18,000 workers at eight North American styrene butadiene rubber plants. The study period begins at industry start-up in 1943 and continues through 1991. Detailed quantitative estimates of exposure to butadiene, styrene, and benzene (a potentil confounding factor at some of the plants) were made for each worker in the study. Both mortality and cancer incidence rates for workers was evaluated.

The results of this study, which were published in 1996, indicate an increase in leukemia associated with working in the styrene-butadiene rubber industry. These increases were most significant in the maintenance and laboratory worker classifications. Although exposure estimates were made and increases are associated with increased exposure to 1,3-

butadiene, lack of information on exact jobs for some workers and the high correlation between butadiene and styrene make the study results difficult to use for quantitative risk assessment.

Additional follow-up studies are being conducted by the University of Alabama and others to determine more accurately how exposures are related to increased risk of leukemia. One key issue is whether butadiene alone, or something else associated with styrene-butadiene rubber production is responsible for the excess. Another question is whether cumulative low dose exposure or intermittent high dose exposure is associated with increased risk. IISRP is also sponsoring a study at the University of Alabama to determine the exact leukemia subtype diagnosis for the leukemia cases. ***Elizabeth Delzell, S.D. is the principal investigator.***

Mutagenicity & Biomarkers

Health Effects Institute (HEI) Research Program

The HEI is sponsoring research on DNA adducts of butadiene and its two major metabolites, the monoepoxide and the diepoxide, and on the carcinogenicity of the diepoxide metabolites. Sponsored studies will define the mutagenic potency and mutational spectra for 1,3-butadiene, and the mono- and diepoxide metabolites. DNA and hemoglobin adduct studies may lead to the development of human biomarkers for use in populations. ***Dr. Debra Kaden is the study coordinator.***

The research sponsored by HEI is conducted at the following research centers:

Mutagenicity

- ***Chemical Industry Institute of Toxicology***

  The goal of this study is to define the relative mutagenicity of the two major butadiene metabolites, the monoepoxide (1,2-epoxy-3-butene) and the diepoxide (1,2,3,4-diepoxybutane), by determining the frequency and types of mutations at several "reporter" genes in transgenic mice, transgenic rats, and in human lymphoblast cells. In order to address in vivo and in vitro extrapolation issues, investigators will also examine the mutagenicity and mutational spectra in transgenic mouse cells (embryonic fibroblasts) exposed in vitro. ***Leslie Recio, Ph.D. is the principal investigator.***

- ***Wadsworth Center for Laboratories & Research New York State Department of Health***

  The goal of this study is to examine the relative mutagenicity of 1,3-butadiene and its two major metabolites, the butadiene monoepoxide (1,2-epoxy-3-butene) and diepoxide (1,2,3,4-diepoxybutane), in rodents. Both the frequency and types of mutations (mutational spectra) in a portion of the endogenous hprt gene will be examined in lymphocytes of rats and mice exposed to 1,3-butadiene and its epoxide metabolites. By comparing the molecular events induced by butadiene and its major metabolites in species that differ in their sensitivity to 1,3-butadiene, this study will help in across-species extrapolations. ***Vernon E. Walker, Ph.D. is the principal investigator.***

Biomarker Development

- ***University of North Carolina***

  HEI is sponsoring the development of an assay for hemoglobin adducts resulting from both the mono- and diepoxide metabolites of butadiene. These adducts will aid in determining the relative amounts of these metabolites that form following butadiene exposure. These adducts may serve as biomarkers to determine the relative amounts of the two metabolites in exposed people. ***James Swenberg, DVM, Ph.D. is the principal investigator.***

- ***Vanderbilt University***

  Vanderbilt University is developing analytical techniques for identifying the major DNA adducts derived from butadiene and its metabolites in the lung and urine of rats and mice. Since mice and rats differ in their sensitivity to the carcinogenicity of butadiene, comparison of the types of adducts and their persistence may assist in assessing the role of the two metabolites in carcinogenicity. In addition, this study may lead to the identification of biomarkers of butadiene exposure. ***Ian A. Blair, Ph.D. is the principal investigator.***

Carcinogenicity of the Diepoxide

- ***Lovelace Respiratory Research Institute***

  This study is testing the hypothesis that the diepoxide metabolite of 1,3-butadiene (1,2,3,4-diepoxybutane) is the causative agent for lung tumors in the mice. By treating both rats and mice with the diepoxide, the study can also determine whether rats are capable of developing lung tumors from sufficiently high diepoxide exposures. The investigators propose to determine whether the diepoxide induces specific mutations in the K-ras gene from both rat and mouse lung tumors. Previous studies have show that following butadiene exposure to mice, many lung tumors contained activated K-ras. If positive, this study will demonstrate that 1,2,3,4-diepoxybutane is the toxic butadiene metabolite and that the same molecular mechanism is operant in mice and rats exposed to the diepoxide. This would help explain the species differences in response to butadiene exposure and aid extrapolation across species. ***Rogene F. Henderson, Ph.D. is the principal investigator.***

Other Research

Research on 1,3-butadiene is also being conducted at several US universities under federal grants. These organizations include the University of Colorado, Harvard University, the University of Texas Medical Branch at Galveston, and the University of Wisconsin. The National Cancer Institute is conducting studies on Chinese petrochemical workers who have occupational exposure to 1,3-butadiene. Shell International is conducting metabolism and biomarker studies in the Netherlands.

Members of the Olefins Panel

Toxicology Research Task Group

These industry scientists provide oversight of the CMA Butadiene Research Program:

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Olefins Panel
Butadiene Research Program

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BP Chemical Company

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